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Analysis of 144 pediatric nosocomial candidaemia episodes over a four-year period

Pediatric nosocomial candidaemia

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Abstract

Aim: The term candidemia simply indicates the presence of Candida species in the blood. Candida spp. are important pathogens in neonatal intensive care unit (NICU) patients, critically ill patients, and those with underlying immunocompromising conditions. Material and Method: In this retrospective study, 144 nosocomial candidemia episodes of 106 pediatric patients who had been admitted to pediatric units of Çukurova Univesity Hospital from 2010 January to 2013 December were evaluated. These 106 children's demographic and clinical features, risk factors, blood and intravascular line cultures, antifungal resistance, treatment and clinical outcome were evaluated. Results: The most frequently isolated species were Candida parapsilosis (31.9%), C. albicans (29.2%). C. tropicalis (16.0%), C. kruseiandC. Famata (4.2%),C. Glabrata (3.5%). Risk factors of 106 pediatric patients with Candidemiae were investigated. The main risk factors for candidemia included the presence of intravascular (IV) lines (68.1%), multiple antibiotics therapy (79.1%), total parenteral nutrition (59.7%), nasogastric tube insertion (45.1%), mechanical ventilation (34.7%), admission to intensive care unit (32.6%), and neutropenia (22.9%). The overall mortality rate of candida species was 17.9%. Discussion: Regular surveillance of local Candida species, resistance profiles, and risk factors are important in order to identify patients at risk and to develop empirical treatment protocols to reduce the incidence and mortality of candidemia.

Keywords

Candida; Risk Factor; Mortality; Childhood

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Introduction

During recent years, fungal infections are reported to constitute an increasing proportion among all nosocomial infections, only preceded by bacterial infections. Regarding invasive fungal infections, *Candida* species are the leading causative agents in hospitalized children. In the United States, *Candida* species are reported as the third leading cause of healthcare-associated bloodstream infections [1,2].

Although the most common agent in *Candidemia* is *C. albicans*, there has been an increasing incidence of non-albicans *Candida* species in recent years [3,4]. Especially among child patients, *C. parapsilosis* and *C. tropicalis* constitute more than half of the non-albicans *Candida* infections [5,6]. According to studies, the most common risk factors for *Candidemia* are broad-spectrum antibiotic use, total parenteral nutrition (TPN), the presence of a central venous catheter, malignancy, chemotherapy, immunosuppressant use, neutropenia, and diabetes [7-9].

Nosocomial fungal infections are an important cause of increased morbidity and mortality. Some causes of increased frequency of fungemia and fungemia-associated mortality are the increasing number of diagnostic and therapeutic interventions applied to patients as a result of the advances in modern medicine, widespread use of treatment regimes that suppress host defense mechanisms, and ever-growing utilization of broad-spectrum anti-bacterial drugs. Among all children with sepsis, fungal infections are the second leading cause of mortality (13%). *Candidemia* is often characterized by symptoms and signs of sepsis [2,3,10-12].

In this study, we aimed to investigate the demographical and clinical features and treatment outcomes of *Candidemia* episodes that developed in patients hospitalized in pediatric wards of Çukurova University Hospital, to determine the predisposing risk factors for the purpose of taking necessary precautions, and to compare epidemiologic variations in nosocomial *candidemia.*

Material and Methods

In this study, we retrospectively examined 144 *candidemia* episodes in 106 patients who were treated as inpatients in intensive care units (pediatric, neonatal, cardiovascular surgery, pediatric surgery, neurosurgery), pediatric hematology and oncology wards, and other pediatric wards from January 2010 to December 2013. A data form was created; each patient's demographical and clinical features, risk factors, blood and catheter culture results, antifungal resistance patterns, treatment, and clinical outcomes were obtained from patient files and were recorded on these data forms. In some patients, antifungal treatment was initiated empirically based on the patient's age, the site of *candida* growth and underlying disease (especially febrile neutropenia); and it was adjusted according to antifungal sensitivity results. The study was approved by the institutional review board.

Candidemia is defined as isolation of a *Candida* species in at least one blood and/or catheter culture in the presence of systemic symptoms and signs. Catheter-associated *Candidemia* is regarded as >15 cfu candida growth in a catheter-tip culture. Utilization of one or more types of antibiotics for more than 14 days, neutropenia (absolute neutrophil count <1000/mm^3), history of surgical operation within the last 30 days, TPN and catheter applications, chemotherapy and malignancy were accepted as risk factors. Deaths occurring within the first 30 days in the presence of clinical, microbiological and/or histological evidence were accepted as *Candidemia*-associated mortality.

All the data were analyzed using SPSS version 20 (SPSS, Chicago, IL, USA) statistics package software. Student t-test and chi-square tests were used for comparison of the groups.

$p < 0.05$ was accepted as the level of statistical significance.

Results

Table 1 shows the demographical and clinical features of 106 patients with *Candidemia* included in this study. Mean age (± SD) was 43± 47 months (median age: 28 months). The male/female ratio was 54/52. Of these patients, 28.8% were admitted to intensive care units and 25.5% were admitted to pediatric hematology and oncology wards.

Table 1. Clinical and Demographical Features of 106 Pediatric Patients with Candidemia Included In the Study

	Patients, (n:106) (%)
Age (month)	
Mean ±SD	43± 47
Median	28
Sex, n(%)	
Male	54 (51)
Female	52 (49)
Place of admission* (n) (%)	
Intensive care units (+)	45 (31.2)
Hematology-oncology wards(+)	40(27.7)
Neonatal intensive care unit (+)	29 (20.1)
Burns unit (+)	10 (6.9)
Other pediatric wards (+)	30(20.8)
Complications (n)(%)	
Endophtalmitis (+)	1 (0.9)
Mortality n(%)	19 (17.9)
0 – 60 months	9(47.3)
0 – 11 months	4(21.0)
12– 60 months	6(31.6)
>60 months	

*Number of patients is calculated based on 144 episodes.

Of the examined patients, 82 (77.3%) were younger than 60 months while 24 (22.7%) were older than 60 months. The general mortality rate was 17.9%. Of those patients who died, 68.4% (n: 13) were younger than 60 months, and 47.3% (n:9) were younger than 12 months.

General mortality rate among cases with *Candidemia* was 17.9%. Mortality rate was higher among children younger than 60 months (68.4%), with *C. albicans* species *(25%)* and *C.nonalbicans* isolates (75%) (Table 7). Only one patient developed endophthalmitis (0.9%) as a complication.

Table 2 summarizes risk factors for *Candidemia.* Main risk factors detected in 106 patients with *Candidemia* examined in our study were: intravascular catheter (68.1%), multiple antibiotherapy (79.1%), total parenteral nutrition (59.7%), nasogastric tube (45.1%), mechanical ventilation (34.7%), admission to intensive care unit (32.6%) and neutropenia (22.9%).

Table 3 shows *Candida* species isolated from blood and catheter cultures. The most frequently isolated *Candida* species are *C. parapsilosis* (31.9%), *C. albicans* (29.2%), and *C.tropicalis* (16.0%).

Table 4 shows the body fluids from which *Candida* species were isolated during *Candidemia* episodes. *Candida* species were isolated from blood culture in 94.4% and from catheter culture in 5.6% of *Candidemia* episodes.

Table 2. Risk factors in pediatric patients based on 144 episodes in 106 patients with Candidemia

Risk Factors	Number of patients, n (%)
Antibiotic use (+)	139(96)
Presence of intravascular catheter (+)	96(68.1)
Total parenteral nutrition (+)	80(59.7)
Presence of nasogastric tube (+)	65(45.1)
Mechanical ventilation (+)	50(34.7)
Admission to intensive care unit (+)	47(32.6)
Presence of urinary catheter (+)	42(29.2)
Neutropenia (+)	33(22.9)
Chemotherapy application (+)	27(18.8)
History of surgical operation (+)	22(15.3)
Steroid use (+)	15(10.4)
Prematurity (+)	14(9.7)
Mucositis (+)	4(2.8)
Diabetes (+)	3 (2.1)
H2 blocker use (+)	23(16)

Table 3. Isolated Candida Species

Candida species	N (%)
C.albicans (+)	42(29.2)
C.parapsilosis (+)	46(31.9)
C.tropicalis (+)	23(16.0)
C.famata (+)	6(4.2)
C.krusei (+)	6(4.2)
C.glabrata (+)	5(3.5)
C.dubliniensis (+)	4(2.8)
C.keyfr (+)	4(2.8)
Other Candida spp. (+)	8(5.6)

Table 4. Sensitivity to fluconazole, and association with mortality among Candida species

Candida spp	n: 144 (%)	Fluconazole (%)			Mortalit ,n(%)
		S	I	R	
C.albicans	42(29.2)	41(97.6)	1 (2.4)	0	5(25)
C.parapsilosis	46(31.9)	46(100)	0	0	7(35)
C.glabrata	5(3.5)	4(80)	1(20)	0	1(5)
C.tropicalis	23(16.0)	23(100)	0	0	3(15)
C.famata	6(4.2)	6 (100)	0	0	0(0)
C.dubliniensis	4(2.8)	4(100)	0	0	0(0)
C.krusei	6(4.2)	2(33.3)	0	4(66.7)	0(0)
C.keyfr	4(2.8)	4(100)	0	0	1(5)
Other Candida spp.	8(5.6)	6(75)	2(25)	0	2 (10)

S: Sensitive I: Intermediate sensitivity R: Resistant

Table 5 shows the results of anti-fungal sensitivity test in isolated Candida species. Totally 7 of the 144 isolates (4.9%) were found to have antifungal resistance, and all of these isolates were NAC species. Amphotericin B resistance was detected in 2 (1.4%) isolates; fluconazole resistance was detected in 4 (2.8%) isolates; and voriconazole resistance was detected in 1 (0.7%) isolate. One isolated *C.parapsilosis* species had resistance against amphotericin B, while another isolated *C.parapsilosis* species had resistance against both amphotericin B and voriconazole.

Table 6 shows sensitivity to fluconazole among Candida species, and the association between Candida species and mortality. All *C. albicans* isolates were sensitive to fluconazole, while 3.9% of *Candida* nonalbicans isolates were resistant against fluconazole. Of the 6 isolates of *C. krusei*, 4 (66.7%) had resistance against fluconazole.

Treatment Outcomes of Patients

Of all patients, 40.6% received fluconazole. According to the guideline on febrile neutropenic patients, 26.2% received amphotericin B, 15.3% received caspofungin, 9.6% received voriconazole, and 2.6% received amphotericin B + flucytosine. For those who had catheter infection, catheter was removed. When the treatment was initiated empirically in febrile neutropenic patients, the treatment was not changed if the antifungal sensitivity test results showed that the growing Candida species was sensitive to the administered drug.

Table 7 shows risk factors responsible for the development of *C. albicans* and *C.nonalbicans* infections. In comparison to *C. albicans,* the major risk factors in *Candida nonalbicans* infections were as follows: mechanical ventilation, presence of the urinary catheter, nasogastric tube placement and admission to intensive care units ($p < 0.01$, $p < 0.05$). Among patients with *Candidemia* who did not receive gastric acid suppression treatment, *C. nonalbicans* infection was more frequent (%75.2) compared to *C. albicans* (%24.8) ($p<0.05$). *C. albicans* infection was significantly more frequent compared to *C.nonalbicans* infection among patients treated in the intensive care unit ($p<0.005$).

Table 5. Anti-Fungal Sensitivity Test Results Among Isolated Species of Candida

Antifungals	Candida albicans (n)(%)			Candida nonalbicans (n) (%)		
	S	I	R	S	I	R
Amfotericin B	41(97.6)	1(2.4)	0	100(97.9)	1 (0.7)	2(1.4)
Fluconazole	41(97.6)	1(2.4)	0	95(93.1)	3 (0.7)	4(2.8)
Voriconazole	42(97.6)	0	0	101(99.3)	0	1(0.7)
Caspofungin	42(97.6)	0	0	102(100)	0	0

S: Sensitive I: Intermediate sensitivity R: Resistant

Table 7. Risk Factors Based On Number of Candida Episodes and Species

Risk Factors	C.albicans (n:42)(%)	C.nonalbicans (n:102) (%)	(p)
Antibiotic use (+)	30(71.4)	99(97)	NS
Total parenteral nutrition (+)	23 (54.7)	63 (61.7)	NS
Presence of intravenous catheter (+)	27 (64.2)	69(67.6)	NS
Chemotherapy (+)	8 (19.)	19(18.6)	NS
Neutropenia (+)	27 (64.2)	69(67.6)	NS
Steroid use (+)	5(11.9)	10(9.8)	NS
Mechanical ventilation (+)	8(19)	42(41.1)	<0.01
Presence of urinary catheter (+)	6(14.2)	36(35.2)	<0.01
Presence of nasogastric tube (+)	13(30.9)	52(50.9)	<0.05
Admission to intensive care unit (+)	9(21.4)	38(37.2)	<0.05
Mucositis (+)	0(0)	4(3.9)	NS
History of surgical operation (+)	5(11.9)	17(16.6)	NS
Diabetes (+)	2(4.7)	1(0.9)	NS
H2 blocker use (+)	12(28.5)	11(10.7)	NS
Prematurity (+)	2(4.7)	12(11.7)	NS

V. Body Fluids From Which Candida Species Were Isolated

Site of growth	Number of patients, n (%)
Blood	136 (94.4)
Catheter	8 (5.6)

Discussion

Candida- associated fungemia takes the lead among all nosocomial fungal infections.

Studies related with *Candidemia* report the major risk factors for the development of these infections as broad-spectrum antibiotic use, total parenteral nutrition, central venous catheter, malignancy, chemotherapy, immunosuppressant drug use, neutropenia and diabetes [7,9]. According to our results, major risk factors for the development of all *Candida* infections were found as multiple antibiotic use (79.1%), the presence of central venous catheter (68.1%), total parenteral nutrition (59.7%), in decreasing order of frequency; and our results seem to be consistent with previous reports. Moreover, in comparison

with patients with *C.albicans* infections, mechanical ventilation (34.7%), the presence of nasogastric tube (45.1%), admission to intensive care unit (32.6%) and presence of urinary catheter (29.1%) were significantly more frequent among patients with *Candida nonalbicans* infections (p<0.05). *Candida* nonalbicans infections were significantly more frequent in comparison to *C.albicans* infection among patients who receive gastric acid suppression treatment (75.2% vs. 24.8%) (p<0.05).

Considering admission rates to intensive care and neonatal intensive care units in our study group (31.2%+20.1%=51.3%), our results are predictable and consistent with the results of previous studies.

Recent studies related with *Candidemia* in child patients show that the proportion of *C.albicans* infection is decreasing, being replaced by *Candida* non-albicans infections [9,11,13,15-17]. In our study, the most frequently isolated *Candida* species during *Candidemia* episodes within the last 3 year was (% 29,2); and the proportion *Candidemia* due to non-albicans *Candida* was 70.8% (Figure 1). Especially between the years 2011 and 2013, we detected an increase in the proportion of *Candida* non-albicans (62.5%-70.8%) infections in comparison to *C.albicans* infections (17.6%-37.5%), which was a finding that is consistent with previous reports (Figure 2).

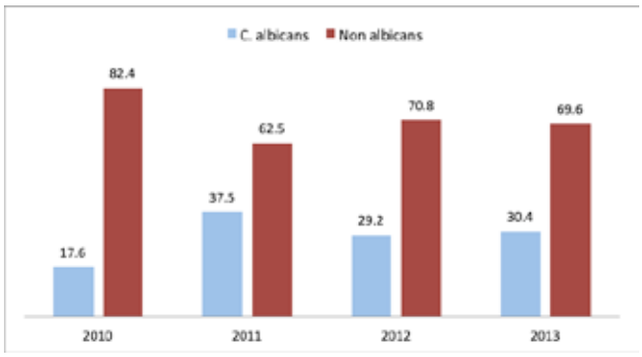

Figure 1. Candidemia episodes within the last 3 year

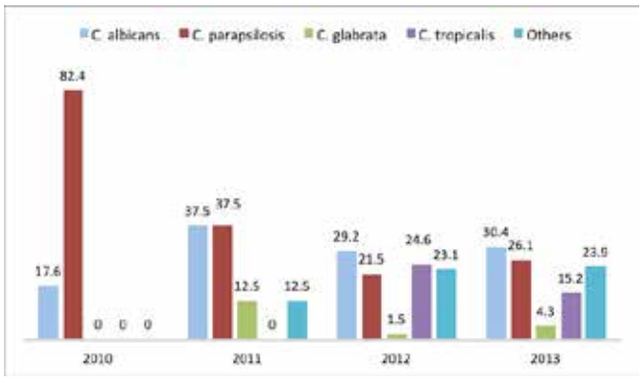

Figure 2. An increase in the proportion of Candida non-albicans infections in comparison to C.albicans infections

Studies report the most frequently isolated non-albicans *Candida* species as *C. tropicalis, C. parapsilosis,C. glabrata* and *C. krusei*. While *C. parapsilosis* takes the lead among *Candidemia* causes in Europe, Canada, and Latin America countries; in the US, the most frequent cause is *C. glabrata* [14]. In their study involving 102 pediatric patients, Çelebi et al. [15] detected C. *albicans* in 39.2%, *C.parapsilosis* in 21.6%, *C. tropicalis* in 15.7%, and *C.glabrata* in 6.9% of patients. In our study, we detected C. *albicans* in 29.2%, *C. parapsilosis* in 31.9%, *C tropicalis* in 16%, and *C glabrata* in 3.2% of our patients, and our rates were similar to theirs (Figure 2, Table 3).

Studies in pediatric age group indicate that fluconazole is effective and safe in treatment of *Candidemia.* Accordingly, 40.6% of the patients in our study group were treated with fluconazole only as the first line of the treatment [18,19]. Additionally, 26.2% of the patients which had febrile neutropenia were treated with amphotericin B, while 15.3% received caspofungin, 9.6% received voriconazole, and 2.6% who had neonatal meningitis were treated with amphotericin B + flucytosine. When the treatment was initiated empirically in febrile neutropenic patients, the treatment was not changed if the antifungal sensitivity test results showed that the growing Candida species was sensitive to the administered drug. Four patients (2.6%) who had ongoing *Candidemia* refractory to treatment were treated with a combination of amphotericin B and fluconazole.

Fluconazole is the most commonly used antifungal for the treatment of invasive *Candida* infections, and resistance against fluconazole and other azoles is an important therapeutic problem. Studies show fluconazole resistance does not exist among *C.albicans* isolates but is present in high rates among *C.nonalbicans* strains such as *C.krusei* (78.5%) and *C.glabrata* (63.16%). In our study, all of the *C.albicans* isolates were sensitive to fluconazole, while 2.8% of *Candida* non-albicans strains showed resistance against fluconazole, and 66.7% of these resistant strains were *C.krusei*. Some authors relate the increasing rate of fluconazole resistance to the fact that it is the first line of a drug in the treatment of *Candida* infection [20].

One study found *Candidemia* associated mortality rate as 42.4%; in that study, the majority of the mortal cases were infected with *Candida* non-albicans isolates and under 1 year of age [21]. Among infants and children, *Candidemia*- associated mortality rate varies in a wide range between 11% and 54% [17,22-24] . The variation in this rate depends on the underlying disease, age and Candida species. In our study, the general mortality rate among cases with *Candidemia* was 17.9%. Mortality rate was 68.4% among children younger than 60 months of age, and 47.3% below 12 months of age. Mortality was higher among patients infected with *Candida* nonalbicans species (75%).

As a conclusion, in order to control nosocomial *Candida* infections and to reduce mortality associated with these infections, it is of vital importance that regular surveillance studies are carried out, predisposing risk factors are taken under control, and empirical treatment schemes are established after determining resistance profiles.

Scientific Responsibility Statement
The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement
All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.
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Conflict of interest
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